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2.3.S.7. STABILITY

This section contains information specific for formulations containing Original drug substance, which are discontinued. For information purposes, data/information supportive of the platform development approach for other presentations is maintained.

2.3.S.7.1. Stability Summary and Conclusions

The commercial shelf life of the BNT162b2 drug substance is 6 months when stored at the intended storage condition of $-20 \pm 5^{\circ}\text{C}$. The shelf life is based on the currently available data from stability studies utilizing material from one batch at the CCI scale manufactured using process 2a, process validation batches manufactured using Process 2 at different manufacturing sites, two emergency supply drug substance batches manufactured using Process 2 and three clinical drug substance batches manufactured using Process 1.

2.3.S.7.1.1. Stability Batches and Studies

The stability program is designed to follow ICH guidelines for stability of drug substance (ICH Guideline Q1A: Stability Testing of New Drug Substances and Products; ICH Guideline Q5C: Quality of Biotechnological Products, Stability Testing of Biotechnological/Biological Products).

To date, 16 process performance qualification drug substance batches have been manufactured at Pfizer Grange Castle, Pfizer Andover, BioNTech Mainz/Rentschler and BioNTech Marburg using the CCI scale using the commercial process (process 2). These batches have been enrolled on formal stability studies as per Table 2.3.S.7-1.

Additionally, three CCI and three CCI scale drug substance batches were enrolled in formal stability programs that include storage under long term and accelerated conditions. These batches have been aliquoted into small volume containers, which are representative of the commercial CCI bags and stored under ICH conditions. The small volume containers represent a worse case with significantly higher surface area per unit solution volume compared to the large-scale commercial containers. Therefore, based on the use of the same product-contact materials of constructions CCI and a worse case dimensional ratio, the small volume containers are an appropriate scaled -down.

One batch manufactured at the CCI scale using process 2a at the Pfizer, Andover site has been included into the stability program.

Two batches of emergency supply drug substance, 20Y513C101 and 20Y513C201, manufactured using the commercial process (Process 2) have been placed on stability and stored under long term, accelerated, and thermal stress conditions in small volume CCI bags. Stability data from these studies are considered to be predictive of the commercial drug substance.

Additionally, three clinical batches of drug substance have been manufactured using Process 1 and placed on stability and stored under long term, accelerated, and thermal stress conditions. These supportive stability batches of drug substance have been stored in

polypropylene tubes which are commonly used for storing aliquots of aqueous solutions as they are inert plastics and were acceptable containers for early phase, supportive stability studies.

Process 2 drug substance manufacturing initially utilized a CCI manufacturing scale. The Process 2 manufacturing was scaled up to CCI at the Andover, MA, Suite J facility. Process 2a manufacturing utilized a CCI. As the drug substance formulation and concentration are not changing, the scale of the manufacturing process is not expected to impact the stability of the resulting drug substance, and the shelf life established for the CCI scale drug substance of 6 months had been applied to the CCI Process 2 and CCI Process 2a scale drug substance batches. The shelf life was confirmed with stability studies initiated on CCI Process 2 and CCI Process 2a drug substance

A summary of all drug substance batches on stability studies and current available stability data are shown in Table 2.3.S.7-1. These status of the stability studies is indicated in the table. Further information on confirmation of the drug substance shelf life is discussed in [Section 3.2.S.7.1. Stability Summary and Conclusions](#).

Table 2.3.S.7-1. Summary of On-going Stability Studies

Batch Number	Date of Manufacture	Batch Use	Study Type	Storage Condition	Available Data	Study Status
Process 2a						
HD5714 (Pfizer Andover, MA Suite J)	May 2023	Clinical , (CCI), Stability	Long Term	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
Process 2						
1086032 (BioNTech Marburg/Rentschler)	March 2022	CCI Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	12 months	On-going
			Accelerated	5 ± 3 °C	6 months	Complete
1086053 (BioNTech Marburg/Rentschler)	March 2022	CCI Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	12 months	On-going
			Accelerated	5 ± 3 °C	6 months	Complete

Table 2.3.S.7-1. Summary of On-going Stability Studies

Batch Number	Date of Manufacture	Batch Use	Study Type	Storage Condition	Available Data	Study Status
1086054 (BioNTech Marburg/ Rentschler)	March 2022	CCI Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	12 months	On-going
			Accelerated	5 ± 3 °C	6 months	Complete
FP5958 (Pfizer, Grange Castle) ^c	December 2021	In process hold, stability ^{c,d}	Long Term	-20 ± 5 °C	12 months	Complete ^e
			Accelerated	5 ± 3 °C	3 months	Complete
FP5960 (Pfizer, Grange Castle)	December 2021	CCI Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	12 months	Complete ^e
			Accelerated	5 ± 3 °C	3 months	Complete
FP5961 (Pfizer, Grange Castle)	December 2021	CCI Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	12 months	Complete ^e
			Accelerated	5 ± 3 °C	3 months	Complete
FT0774 (Pfizer, Grange Castle)	December 2021	CCI Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	12 months	Complete ^e
			Accelerated	5 ± 3 °C	3 months	Complete

Table 2.3.S.7-1. Summary of On-going Stability Studies

Batch Number	Date of Manufacture	Batch Use	Study Type	Storage Condition	Available Data	Study Status
FH7784 (Pfizer Andover, MA)	July 2021	CCI Scale, Process performance qualification Stability Process 2	Long Term	-20 ± 5 °C	24 months ^a	Complete
			Accelerated	5 ± 3 °C	6 months ^a	Complete
FJ1355 (Pfizer Andover, MA)	August 2021	CCI Scale, Process performance qualification Stability Process 2	Long Term	-20 ± 5 °C	24 months ^a	Complete
			Accelerated	5 ± 3 °C	6 months ^a	Complete
FJ5358 (Pfizer Andover)	August 2021	CCI Scale, Process performance qualification Stability Process 2	Long Term	-20 ± 5 °C	24 month ^a	Complete
			Accelerated	5 ± 3 °C	6 month ^a	Complete
FM3506 (Pfizer Andover, MA Suite J)	October 2021	CCI Commercial supply, Annual	Long Term	-20 ± 5 °C	24 months	Complete
2234486- MB0001 (BNT Marburg)	February 2021	Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	6 months	Complete
2234486- MB0002 (BNT Marburg)	February 2021	Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 month	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	6 months	Complete
2234486- MB0003 (BNT Marburg)	February 2021	Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 month	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	6 months	Complete
EP3345 (Pfizer, Andover, Building B, Suite J)	January 2021	Commercial supply, Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 month	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	1 week	Complete
			Low Temperature	-90 to -60 °C	1 month	Complete
20E162001 (1071539) (BNT Mainz, Rentschler)	September 2020	Emergency supply ^a , Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	1 month	Complete
			Low Temperature	-80 to -60 °C	1 month	Complete
			Thermal Cycling Study 4-6		6 months	Complete

Table 2.3.S.7-1. Summary of On-going Stability Studies

Batch Number	Date of Manufacture	Batch Use	Study Type	Storage Condition	Available Data	Study Status
20E162002 (1071542) (BNT Mainz, Rentschler)	September 2020	Emergency supply ^b , Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	1 month	Complete
			Low Temperature	-80 to -60 °C	1 month	Complete
20E162003 (1071544) (BNT Mainz, Rentschler)	October 2020	Emergency supply ^a , Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	1 month	Complete
			Low Temperature	-80 to -60 °C	1 month	Complete
20Y513C701 (Pfizer, Andover, ACMF)	September 2020	Emergency supply ^a , Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	1 month	Complete
			Low Temperature	-90 to -60 °C	1 month	Complete
			Thermal Cycling Study 3		12 months	On-going
			Thermal Cycling Study 2		12 months	On-going
20Y513C601 (Pfizer, Andover, ACMF)	September 2020	Emergency supply ^a , Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	1 month	Complete
			Low Temperature	-90 to -60 °C	1 month	Complete
			Thermal Cycling Study 1		12 months	On-going
			Photostability		Dark Control and Light Exposed	Complete
20Y513C501 (Pfizer, Andover, ACMF)	September 2020	Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	1 month	Complete
			Low Temperature	-90 to -60 °C	1 month	Complete
20Y513C401 (Pfizer, Andover, ACMF)	August 2020	Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
20Y513C301 (Pfizer, Andover, ACMF)	August 2020	Emergency supply ^a , Process performance qualification, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
20Y513C201 (Pfizer,	August 2020	Emergency supply ^a ,	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete

Table 2.3.S.7-1. Summary of On-going Stability Studies

Batch Number	Date of Manufacture	Batch Use	Study Type	Storage Condition	Available Data	Study Status
Andover, ACMF)		Stability	Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	1 month	Complete
			Low Temperature	-90 to -60 °C	1 month	Complete
20Y513C101 (Pfizer, Andover, ACMF)	July 2020	Emergency supply ^b , Clinical inventory, Stability	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5% RH	1 month	Complete
			Low Temperature	-90 to -60 °C	1 month	Complete
Process 1						
R443-P020.2-DS (BNT)	June 2020	Stability, Clinical	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	24 months	Complete
			Thermal Stress	25 ± 2 °C	6 months	Complete
R438-P020.2-DS (BNT)	May 2020	Stability, Clinical	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	24 months	Complete
			Thermal Stress	25 ± 2 °C	6 months	Complete
R427-P020.2-DS (BNT)	April 2020	Stability, Clinical	Long Term	-20 ± 5 °C	24 months	Complete
			Accelerated	5 ± 3 °C	24 months	Complete
			Thermal Stress	25 ± 2 °C	6 months	Complete

- a. Due to the implementation of a new sample handling process enrollment is at approximately 3 months from the date of manufacture.
- b. Emergency supply designation applies to U.S. market
- c. Batch FP5958 was initially included to support a maximum cumulative hold at commercial scale at Pfizer, Grange Castle, 3.2.S.2.5- Process validation and or Evaluation- Hold Times (Grange Castle).
- d. An additional supportive cumulative hold batch GP6836 was placed on stability at Pfizer, Grange Castle, 3.2.S.7.1- Stability Summary and Conclusions, Omicron (BA.4/BA.5)
- e. Stability studies have been terminated after the 12 month timepoint for batches FP5958, FP5960, FP5961 and FT0774 due to OOS results at 9 and 12 month timepoints. Refer to 3.2.S.7.1 Stability Summary and Conclusions.
- f. Batch HD5714 was enrolled on stability to support manufacturing process 2a.
- Abbreviations: RH= relative humidity

2.3.S.7.1.2. Study Protocol for Drug Substance Batches at the Long Term Condition (-20 °C)

Aliquots of Pfizer, Andover, Suite J manufactured at the CCI Scale Process 2a drug substance batches have been stored at -20 ± 5 °C. Testing is being performed according to the protocol indicated in Table 2.3.S.7-2.

Table 2.3.S.7-2. Stability Protocol Process 2a Drug Substance Batch Stored at 20 ± 5 °C (Long Term Storage Condition)

Analytical Procedure	Test Intervals ^a
Appearance (Clarity)	0, 1M, 2M, 3M, 6M
Appearance (Coloration)	0, 1M, 2M, 3M, 6M
Potentiometry	0, 1M, 2M, 3M, 6M
Content (RNA Concentration) (UV Spectroscopy)	0, 1M, 2M, 3M, 6M
RNA Integrity (Capillary Gel Electrophoresis)	0, 1M, 2M, 3M, 6M
5'-Cap (RP-HPLC)	0, 1M, 2M, 3M, 6M
Poly (A) Tail (ddPCR)	0, 1M, 2M, 3M, 6M
Endotoxin (LAL) ^b	0, 6M
Bioburden ^b	0, 6M

a. Initial data (t=0) are from release testing.

b. Endotoxin and Bioburden testing also performed at the expiry timepoint.

Abbreviations: M = Month; UV = ultraviolet; RP-HPLC = reverse phase high performance liquid chromatography; ddPCR = droplet digital polymerase chain reaction; LAL = Limulus amoebocyte lysate

Aliquots of BioNTech Marburg/Rentschler drug substance manufactured at the CCI scale Process 2 have been stored at -20 ± 5 °C. Testing is being performed according to the protocol indicated in Table 2.3.S.7-3.

Table 2.3.S.7-3. Stability Protocol for BioNTech Marburg/Rentschler CCI Scale Drug Substance Process 2 Batches Stored at -20 ± 5 °C (Long Term Storage Condition)

Analytical Procedure	Test Intervals ^a
Appearance (Clarity)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Appearance (Coloration)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Potentiometry	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Content (RNA Concentration) (UV Spectroscopy)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
RNA Integrity (Capillary Gel Electrophoresis)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
5'-Cap (RP HPLC)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Poly (A) Tail (ddPCR)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Endotoxin (LAL)	0, 24M
Bioburden	0, 24M

a. Initial data (t=0) are from release testing.

Abbreviations: M = Month; UV = ultraviolet; RP-HPLC = reverse phase high performance liquid chromatography; ddPCR = droplet digital polymerase chain reaction; LAL = Limulus amoebocyte lysate

Aliquots of Pfizer drug substance manufactured at the CCI scale process 2 as part of the initial process Validation for Pfizer Grange Castle have been stored at $-20 \pm 5^\circ\text{C}$. Testing is being performed according to the protocol indicated in Table 2.3.S.7-4.

Table 2.3.S.7-4 Stability Protocol for Pfizer Grange Castle Drug Substance Initial Process Performance Qualification Process 2 Batches Stored at $20 \pm 5^\circ\text{C}$ (Long Term Storage Condition)

Analytical Procedure	Test Intervals ^a
Appearance (Clarity)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Appearance (Coloration)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Potentiometry	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Content (RNA Concentration) (UV Spectroscopy)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
RNA Integrity (Capillary Gel Electrophoresis)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
5'-Cap (RP-HPLC)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Poly (A) Tail (ddPCR)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Endotoxin (LAL) ^b	0, 24M
Bioburden ^b	0, 24M

a. Initial data (t=0) are from release testing.

b. Endotoxin and Bioburden testing also performed at the expiry timepoint.

c. Change control raised for the termination of long term stability studies after the 12 month timepoint for process validation batches FP5958, FP5960, FP5961 and FT0774.

Abbreviations: M = Month; UV = ultraviolet; RP-HPLC = reverse phase high performance liquid chromatography; ddPCR = droplet digital polymerase chain reaction; LAL = Limulus amoebocyte lysate

Aliquots of Pfizer, Andover, Suite J manufactured at the CCI Scale Process 2 drug substance batches have been stored at $-20 \pm 5^\circ\text{C}$. Testing is being performed according to the protocol indicated in Table 2.3.S.7-5.

Table 2.3.S.7-5. Stability Protocol for Pfizer, Andover CCI Scale Process 2 Drug Substance Batches Stored at $-20 \pm 5^\circ\text{C}$ (Long Term Storage Condition)

Analytical Procedure	Test Intervals ^a
Appearance (Clarity)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Appearance (Coloration)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Potentiometry	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Content (RNA Concentration) (UV Spectroscopy)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
RNA Integrity (Capillary Gel Electrophoresis)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
5'-Cap (RP-HPLC)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Poly (A) Tail (ddPCR)	0, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Endotoxin (LAL) ^b	0, 24M and end of shelf life
Bioburden ^b	0, 24M and end of shelf life

a. Initial data (t=0) are from release testing.

b. Endotoxin and Bioburden testing also performed at the expiry timepoint.

Abbreviations: M = Month; UV = ultraviolet; RP-HPLC = reverse phase high performance liquid chromatography; ddPCR = droplet digital polymerase chain reaction; LAL = Limulus amoebocyte lysate

Aliquots of Pfizer, Andover drug substance batches manufactured at the CCI scale have been stored at $-20 \pm 5^\circ\text{C}$. Testing is being performed according to the protocol indicated in Table 2.3.S.7-6.

Table 2.3.S.7-6. Stability Protocol for Pfizer, Andover Drug Substance CCI Scale Process 2 Primary Batches Stored at $-20 \pm 5^\circ\text{C}$ (Long Term Storage Condition)

Analytical Procedure	Test Intervals ^{a,c,d,f}
Appearance (Clarity)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Appearance (Coloration)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Potentiometry	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Content (RNA Concentration) (UV Spectroscopy)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
RNA Integrity (Capillary Gel Electrophoresis)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
5'-Cap (RP-HPLC) ^b	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Poly (A) Tail (ddPCR) ^b	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Endotoxin (LAL)	0, 24M ^c
Bioburden	0, 24M ^c

- Initial data (t=0) are from release testing.
 - Testing performed only on primary batches
 - 1W, 2W and 2M testing not performed on 20Y513C301 and 20Y513C401
 - 1W and 2W testing not performed on EP3345, 20Y513C601 and 20Y513C701
 - 12M testing being performed on batch EP3345. 6M and 12M testing also performed on batch 20Y513C201
 - 1W, 2W and 9M testing not performed on FM3506
- Abbreviations: W = Week; M = Month; UV = ultraviolet; RP-HPLC = reverse phase high performance liquid chromatography; ddPCR = droplet digital polymerase chain reaction; LAL = Limulus amoebocyte lysate

Aliquots of BioNTech Mainz/Rentschler manufactured drug substance batches (process 2) have been stored at $-20 \pm 5^\circ\text{C}$. Testing is being performed according to the protocol indicated in Table 2.3.S.7-7.

Table 2.3.S.7-7. Stability Protocol for BioNTech Mainz/Rentschler Drug Substance Process 2 Primary Batches Stored at -20 ± 5 °C (Long Term Storage Condition)

Analytical Procedure	Test Intervals ^a
Appearance (Clarity)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Appearance (Coloration)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Potentiometry	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Content (RNA Concentration) (UV Spectroscopy)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
RNA Integrity (Capillary Gel Electrophoresis)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Endotoxin (LAL)	0, 24M
Bioburden	0, 24M

a. Initial data (t=0) are from release testing.

Abbreviations: W = Week; M = Month; UV = ultraviolet; RP-HPLC = reverse phase high performance liquid chromatography; ddPCR = droplet digital polymerase chain reaction; LAL = Limulus amoebocyte lysate

Aliquots of BioNTech Marburg manufactured drug substance batches (process 2) have been stored at -20 ± 5 °C. Testing is being performed according to the protocol indicated in Table 2.3.S.7-8.

Table 2.3.S.7-8. Stability Protocol for BioNTech Marburg Drug Substance Process 2 Batches Stored at -20 ± 5 °C (Long Term Storage Condition)

Analytical Procedure	Test Intervals ^a
Appearance (Clarity)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Appearance (Coloration)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Potentiometry	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Content (RNA Concentration) (UV Spectroscopy)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
RNA Integrity (Capillary Gel Electrophoresis)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
5'-Cap (RP HPLC)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Poly (A) Tail (ddPCR)	0, 1W, 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Endotoxin (LAL)	0, 24M
Bioburden	0, 24M

b. Initial data (t=0) are from release testing.

Abbreviations: W = Week; M = Month; UV = ultraviolet; RP-HPLC = reverse phase high performance liquid chromatography; ddPCR = droplet digital polymerase chain reaction; LAL = Limulus amoebocyte lysate

Aliquots of BioNTech Mainz manufactured drug substance batches (Process 1) were stored at -20 ± 5 °C. Testing is being performed according to the protocol indicated in [Table 2.3.S.7-9](#).

Table 2.3.S.7-9. Stability Protocol for BioNTech Mainz Drug Substance Batches Stored at -20 ± 5 °C

Analytical Procedure	Test Intervals (Months) ^a
RNA Content (UV Spectroscopy)	0, 3, 6, 9, 12, 18, 24
RNA Integrity (Capillary Gel Electrophoresis)	0, 3, 6, 9, 12, 18, 24

a. Initial data (t0) are from release testing.

Abbreviations: UV = ultraviolet

2.3.S.7.1.3. Study Protocol for Drug Substance Batches at the Accelerated Condition

To support manufacturing process, hold conditions and to study the effects of temporary excursions above the recommended storage conditions, drug substance aliquots have been stored at 5 ± 3 °C. Protocols are detailed in [Section 3.2.S.7.1 Stability Summary and Conclusions](#).

2.3.S.7.1.4. Study Protocol for Drug Substance Batches at the Thermal Stress and Low Temperature Support Conditions

To support manufacturing process hold conditions and to study the effects of high temporary excursions from the recommended storage conditions, drug substance aliquots are being stored at 25 ± 2 °C and testing is being performed according to the protocol indicated in Section 3.2.S.7.1 Stability Summary and Conclusions.

To support manufacturing process hold conditions and to study the effects of low temporary excursions from the recommended storage conditions, drug substance aliquots of the batches manufactured by Pfizer are being stored at -90 to -60 °C and batches manufactured by BioNTech Mainz/Rentschler at -80 to -60 °C. Testing is being performed according to the protocol indicated in Section 3.2.S.7.1 Stability Summary and Conclusions.

Thermal cycling studies have also been initiated and are being performed per the protocols detailed in Section 3.2.S.7.1 Stability Summary and Conclusions.

2.3.S.7.1.5. Summary of Stability Data

2.3.S.7.1.5.1. Summary of Stability Data at the Long Term Storage Condition

Stability data from the batches stored at the long term condition of -20 ± 5 °C are presented in [Section 3.2.S.7.3 Stability Data – Long Term](#). Up to 24 months of data are available at this condition for Process 1 batches manufactured by CCI, up to 24 months of data are currently available for CCI scale primary stability batches manufactured by Pfizer Andover, BioNTech Mainz/Rentschler, and BioNTech (Marburg) (Process 2), up to 12 months results for process performance batches manufactured by BioNTech Marburg/Rentschler at CCI scale using process 2 and for the process validation campaign at CCI (Process 2) at Pfizer Grange Castle. Drug substance batches manufactured by Pfizer Andover at the CCI scale are enrolled in formal stability studies that include the long term condition of -20 ± 5 °C, with data from the 18 month timepoint available at this time.

The process 2a drug substance batch manufactured at the CCI scale is enrolled in formal stability studies that include the long term condition of $-20 \pm 5^{\circ}\text{C}$, with data from the 3 month timepoint available at this time.

2.3.S.7.1.5.2. Summary of Stability Data at the Accelerated Condition

Stability data from the batches stored at the accelerated condition of $5 \pm 3^{\circ}\text{C}$ are presented in [Section 3.2.S.7.3 Stability Data – Accelerated](#). Up to 24 months of data are available at this condition for Process 1 batches manufactured by CCI (Process 1), up to 6 months of data are currently available for primary CCI (Process 2) drug substance stability batches manufactured by Pfizer, Andover, BioNTech Marburg, BioNTech Mainz/Rentschler and BioNTech Marburg/Rentschler at CCI scale using Process 2 and up to 3 months data is available for the CCI campaign using Process 2 at Pfizer Grange Castle. Drug substance batches manufactured at the CCI scale were enrolled in formal stability studies that include the accelerated $5 \pm 3^{\circ}\text{C}$, with up to 6 months of data available. The process 2a drug substance batch manufactured at the CCI scale was enrolled in formal stability studies that include the accelerated condition of $5 \pm 3^{\circ}\text{C}$ with up to 3 months of data available.

2.3.S.7.1.5.3. Summary of Stability Data at the Thermal Stress Condition

Stability data from the batches stored at the thermal stress condition of $25 \pm 2^{\circ}\text{C}$ are presented in [Section 3.2.S.7.3 Stability Data – Thermal Stress](#). Up to 1 month of data are available for Process 2 batches manufactured by Pfizer BioNTech Mainz/Rentschler and BioNTech Marburg. Additionally, there is up to 6 months of data available for the three batches manufactured by CCI (Process 1).

Out of specification RNA integrity results were generated against the specification in place at the time of testing at the 1 month timepoint for Process 2 batches 20Y513C101, 20Y513C201, 20Y513C701, 20Y513C601, 2234486-MB0002 and 2234486-MB0003 and at the 3 month time point for CCI batches R427-P020.2-DS, R438-P020.2-DS and R443-P020.2-DS when stored at the thermal stress condition of $25 \pm 2^{\circ}\text{C}$. (The results reported for the Process 1 supportive batches were generated using an early phase integration method in place for the Process 1 supportive drug substance batches). Additionally, the RNA Integrity was out of the tightened commercial specification of CCI at the 1 week time point for Process 2 primary drug substance batches 2234486-MB0001, EP3345, 20E162001, 20E162002, 20E162003 and 20Y513C201 at the 2 week timepoint for batches 2234486-MB0002, 20Y513C701, 20Y513C601 and 20Y513C501 and at the 1 month time point for 2234486-MB0003. As the release value generated for RNA Integrity of batch 20Y513C101 was below the tightened commercial specification of CCI all stability data was also out of this specification. A trend in an increase in concentration over the 1 month time was also seen for RNA concentration on Pfizer batches 20Y513C701, 20Y513C601, 20Y513C501, 20Y513C201 and 20Y513C101, however all results remained within the specifications in place at the time of testing as well as the proposed commercial specifications, with the exception of batch 20Y513C201, which was out of specifications at the 1 month time point for RNA concentration. All other data generated to date remained within the clinical acceptance criteria and the proposed commercial acceptance criteria, where applicable. It is not unexpected to generate out of specification results for stressed stability conditions and

this demonstrates the stability indicating properties of the analytical methods, therefore the out of specification results do not impact the overall stability study.

Stability data from the batches stored at the low temperature support condition of -90 to -60 °C or -80 to -60°C are presented in Section 3.2.S.7.3 Stability Data – Thermal Stress. Up to 1 month of data are available for six stability batches manufactured by Pfizer and on three batches manufactured by BioNTech/Rentschler (studies have completed). All data remained within the acceptance criteria in place at the time of testing. All batches were also within all proposed commercial specifications with the exception of batches 20Y513C701 and 20E162003, which were out of specification at the 1 month time point, and batch 20Y513C101 (all results were out of the proposed commercial specification of CCI for RNA Integrity. The out of proposed commercial specification result for batch 20Y513C701 and 20E162003 are likely due to method variability (refer to discussion in [Section 3.2.S.7.1 Stability Summary and Conclusions](#) regarding impact of method variability). As batch 20Y513C101 was manufactured prior to manufacturing optimization that occurred to increase the RNA integrity of the material and the release value of RNA Integrity was below the proposed commercial specification of CCI it is not unexpected that these stability studies had out of specification results and these lots are still considered to be supportive of the stability of the drug substance.

Process validation drug substance batches are being subjected to different thermal cycling studies. Stability data up to 6 months is currently available for the 3 thermal cycling studies initiated on Pfizer process validation drug substance batches 20Y513C701 and 20Y513C601. To date, all data remained within the clinical acceptance criteria in place at the time of testing, and the proposed commercial specifications, where applicable for thermal cycling study 2. The RNA integrity value was out of the proposed commercial specifications at the 21 day time point for thermal cycling study 1 and at the 6 month time point for thermal cycling study 3. As these studies subjected the drug substance material to 2 to 3 cycles of 3 days at the thermal stress condition of 25 ± 2 °C/ 60 ± 5 %RH as a part of the studies, it is not unexpected that out of specification results were seen. Results will continue to be monitored for future time points on these studies.

The results for up to 6 months of the thermal cycling study carried out for batch 20E162001 manufactured at BioNTech Mainz and Rentschler did not show significant changes in the results compared to the initial values, except for Poly(A) tail. The result at 6 months for Poly(A) tail dropped from CCI but this is still within the acceptance criterion CCI

2.3.S.7.1.5.4. Summary of Stability Data at the Photostability Storage Condition

One process validation drug substance batch has been subjected to the ICH photostability condition (option 2). Drug substance bags were exposed to a light source that provided an overall illumination of not less than 1.2 million lux hours and an integrated ultraviolet energy of not less than 200 watt hours/m², per ICH Q1B. Dark control samples were wrapped in aluminum foil to prevent exposure to light. All samples were stored 25 ± 2 °C/ 60 ± 5 % RH for the duration of the study. Comparison between the drug substance exposed to light and the dark control samples show no significant changes for any of the quality attributes

evaluated. The percent RNA integrity was slightly lower than the dark control sample, however, both results were within the specification in place at the time of testing.

Results from this study demonstrate that drug substance is not photolabile at the ICH photostability conditions. The photostability study is complete.

2.3.S.7.1.6. Conclusions for Shelf Life and Storage

The shelf life for the BNT162b2 drug substance is 6 months when stored at the recommended temperature of -20 ± 5 °C in CCI bags.

The shelf life is based on:

- Up to 6 months of current available stability data generated in CCI scale manufactured using Process 2a.
- Up to 24 months of current available stability data generated using CCI scale, up to 18 months using CCI and CCI scale substance manufactured using Process 2.
- Up to 24 months of current available stability data generated using drug substance manufactured using Process 1.
- Comparability demonstrated between Process 1, Process 2 and Process 2a drug substance.
- Understanding of the mRNA platform to support the initial shelf life.

The shelf-life of 6 months established for drug substance manufactured on CCI scale by process 2 is confirmed by real-time data covering at least the established shelf-life for any scale up to CCI used for process 2. In addition, there are 6-months results of one confirmatory batch manufactured at CCI using process 2a. The drug substance formulation, concentration, and container closure are not changing between the different batch scales nor the processes. All data remained within the acceptance criteria in place at the time of testing, and the commercial specifications.

No photostability study was performed on the new 2a process because there was no change in the container closure system. Since the container closure remains the same, the conditions affecting the photostability of the product are unchanged. Therefore, the photostability profile determined during the initial studies for the process 2 remains applicable to the product manufactured under the new 2a process.

Additional drug substance batches representative of the commercial process may be placed on stability in the future.

2.3.S.7.3. Stability Data

Stability data for long term conditions, accelerated condition, thermal stress and photostability studies are provided in Section 3.2.S.7.3.Stability Data.

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